

antigens)

L13 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2001 ACS
 ACCESSION NUMBER: 1995:546956 CAPLUS
 DOCUMENT NUMBER: 122:274119
 TITLE: Hydrophobic polymeric pharmaceutical
 microparticles
 INVENTOR(S): Andrianov, Alexander K.; Langer, Robert S.
 PATENT ASSIGNEE(S): Virus Research Institute, USA; Massachusetts
 Institute of Technology
 SOURCE: PCT Int. Appl., 33 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9508320	A1	19950330	WO 1994-US10692	19940921
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5500161	A	19960319	US 1993-124816	19930921
CA 2172040	AA	19950330	CA 1994-2172040	19940921
AU 9478001	A1	19950410	AU 1994-78001	19940921
EP 720471	A1	19960710	EP 1994-928640	19940921
EP 720471	B1	20010418		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				

PRIORITY APPLN. INFO.: US 1993-124816 A 19930921
 WO 1994-US10692 W 19940921

AB A method for the prepn. of microparticles, and the product thereof, that include dispersing a substantially water insol. non-ionic or ionic polymer in an aq. soln. in which the substance to be delivered is also dissolved, dispersed or suspended, and then coagulating the polymer together with the substance by impact forces to form a microparticle. In an alternative embodiment, the microparticle is formed by coagulation of an aq. polymeric dispersion through the use of electrolytes, pH changes, org. solvents in low concns. (the minimal amt. necessary to break up the dispersion), or temp. changes to form polymer matrixes encapsulating biol. materials. Thus 60 mg of fluorescein-labeled bovine serum albumin was dissolved in 3 mL of 30% aq. soln. dispersion of Eudragite NE 30D and then spraying the aq. dispersion in a flask contg. 200 mL of deionized water using

Turbotack air-atomizing nozzle. The flow rate of the polymeric dispersion was 150. μ L/min, the air pressure was 25 psi, and the distance between the nozzle and surface of water was 30 cm. The resulting microparticles were spherical with an av. diam. of 1-10 μ m and encapsulation efficiency of 65%.

IT 34346-01-5, Glycolic acid-lactic acid copolymer

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrophobic polymeric pharmaceutical microparticles)

L13 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1995:467421 CAPLUS

DOCUMENT NUMBER: 122:222580

TITLE: Adjuvanticity and protective immunity elicited by *Bordetella pertussis* antigens encapsulated in poly(DL-lactide-co-glycolide) microspheres

AUTHOR(S): Shahin, Roberta; Leef, Mary; Eldridge, John; Hudson, Michael; Gilley, Richard

CORPORATE SOURCE: Lab. Pertussis, Cent. Biol. Eval., Bethesda, MD, USA

SOURCE: Infect. Immun. (1995), 63(4), 1195-200
CODEN: INFIBR; ISSN: 0019-9567

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Purified *Bordetella pertussis* antigens, encapsulated in biodegradable poly(DL-lactide-co-glycolide) (DL-PLG)

microspheres, were evaluated for their immunogenicity and ability to elicit a protective immune response against *B. pertussis* respiratory infection. Microencapsulated *pertussis* toxoid, filamentous hemagglutinin, and pertactin all retained their immunogenicity when administered parenterally. Intranasal immunization with a low dose (1 μ g) of encapsulated filamentous hemagglutinin, *pertussis* toxoid, or pertactin elicited strong specific IgG and IgA antibody responses in respiratory secretions that were greater in magnitude than the responses elicited by the same doses of unencapsulated antigen. Intranasal immunization with as little as 1 μ g of encapsulated *pertussis* antigen prior to infection reduced the bacterial recovery by 3 log₁₀ CFU. However, intranasal immunization with the same low doses of unencapsulated antigens did not reduce infection. Intranasal administration of a combination of 1 μ g of each of the microencapsulated *pertussis* antigens was more effective in reducing bacterial infection than administration of any single microencapsulated antigen. Intranasal

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administration of microencapsulated B. **pertussis**
antigens elicits high levels of specific antibody coinciding
with protection against infection when these microspheres are
administered to the respiratory tract. These data provide evidence
of the respiratory adjuvanticity of three different DL-PLG
microsphere preps., each of which contains a unique b.
pertussis antigen.

IT 26780-50-7

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adjuvanticity and protective immunity by Bordetella
pertussis antigens encapsulated in poly
(DL-lactide-co-glycolide)
microspheres)

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO, TOXLIT,
TOXLINE, PHIC, PHIN' ENTERED AT 15:06:47 ON 04 JUN 2001)

L14 31 S L12

L15 23 S L14 NOT L9

L16 17 DUP REM L15 (6 DUPLICATES REMOVED)

L16 ANSWER 1 OF 17 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

ACCESSION NUMBER: 2000-205407 [18] WPIDS

DOC. NO. CPI: C2000-063253

TITLE: Microparticles with adsorbent surface comprising
polymer and detergent, used as vaccines, and for
targeted delivery of e.g. polypeptides, efficient
adsorbance of biologically active macromolecules.

DERWENT CLASS: A14 A23 A26 A96 B04 B07 C03 D16

INVENTOR(S): BARACKMAN, J; KAZZAZ, J; O'HAGEN, D; OTT, G S;
SINGH, M

PATENT ASSIGNEE(S): (CHIR) CHIRON CORP

COUNTRY COUNT: 87

PATENT INFORMATION:

PATENT NO KIND DATE WEEK LA PG

WO 2000006123 A1 20000210 (200018)* EN 59

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC
MW NL OA PT SD SE SL SZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES
FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK
LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG
SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW

AU 9952452 A 20000221 (200029)

EP 1100468 A1 20010523 (200130) EN

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK
NL PT RO SE SI

Searcher : Shears 308-4994

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000006123	A1	WO 1999-US17308	19990729
AU 9952452	A	AU 1999-52452	19990729
EP 1100468	A1	EP 1999-937664	19990729
		WO 1999-US17308	19990729

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9952452	A Based on	WO 200006123
EP 1100468	A1 Based on	WO 200006123

PRIORITY APPLN. INFO: US 1999-285855 19990402; US 1998-124533
19980729

AN 2000-205407 [18] WPIDS

AB WO 200006123 A UPAB: 20000412

NOVELTY - Microparticles with an adsorbent surface are new and comprise:

(1) polymer chosen from poly(alpha -hydroxy acid), polyhydroxy butyric acid, polycaprolactone, polyorthoester, polyanhydride or polycyanoacrylate; and

(2) detergent.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method of producing microparticles with adsorbent surface to which biologically active macromolecule has been adsorbed.

ACTIVITY - Vaccine; immunomodulating. Microparticle induction of immune response was examined in guinea pigs following intramuscular immunization. Five formulations were tested: (1) PLG/CTAB gp 120 adsorbed (25 mu g); (2) PLG/CTAB gp 120 adsorbed (25 mu g) + aluminum phosphate; (3) soluble gp 120 DNA (25 mu g) + aluminum phosphate; (4) soluble gp 120 DNA (25 mu g) alone; and (5) MF59 protein (50 mg). GMT of serum was as follows: (1) 1,435 plus or minus 383; (2) 3,624 plus or minus 454; (3) 119 plus or minus 606; (4) 101 plus or minus 55; and (5) 3,468 plus or minus 911. Antibody induction (collection and analysis of serum) were performed and geometric mean titer of serum determined.

USE - Used for diagnosis or treatment of disease, as vaccines and to raise and immune response. Used to deliver polypeptides, polynucleotides, polynucleosides, **antigens**, pharmaceuticals, hormones, enzymes, transcription or translation mediators, intermediates in metabolic pathway, immunomodulators or adjuvants including aluminum salts (claimed) such as double- and single stranded sequences including cDNA, prokaryotic or eukaryotic mRNA, genomic RNA and DNA sequences form viral or prokaryotic DNA

(RNA and DNA viruses), and synthetic DNA sequences, base analogs of DNA and RNA, antibiotics, antivirals, peptides, oligopeptides, dimers, multimers, **antigens** derived from bacteria (*Bordetella pertussis*, *Neisseria meningitides* (A, B, C, Y), *Neisseria gonorrhoeae*, *Helicobacter pylori* and/or *Haemophilus influenzae*), viruses, parasites, fungi and tumors, non-steroidal anti-inflammatory drugs, analgesics, vasodilators, cardiovascular drugs, psychotropics, neuroleptics, antidepressants, anti-Parkinson drugs, beta blockers, calcium channel blockers, bradykinin inhibitors, angiotensin-converting enzyme inhibitors, prolactin inhibitors, steroids, hormone antagonists, antihistamines, serotonin antagonists, heparin, chemotherapeutic agents, antineoplastics and growth factors (platelet derived growth factor (PDGF), epithelial growth factor (EGF), KGF, insulin-like growth factor (IGF)-1, IGF-2), FGF, polynucleotides that encode therapeutic or immunogenic proteins, immunogenic proteins and epitopes for use in vaccines, hormones including peptide hormones (insulin, proinsulin, growth hormone, GHRH, luteinizing hormone releasing hormone (LHRH), EGF, somatostatin, SNX-111, BNP, insulinotropin, ANP, FSH, LH, PSH and hCG), gonadal steroid hormones (androgens, estrogens, progesterone), thyroid-stimulating hormone, inhibin, cholecystokinin, ACTH, CRF, dynorphins, endorphins, endothelin, fibronectin fragments, galanin, gastrin, glucagons, GTP-binding protein fragments, guanylin, leukokinins, magainin, mastoparans, dermaseptin, systemin, neuromedin, neurotensin, pancreastatin, pancreatic polypeptide, substance P, secretin, thymosin, and cytokines (interleukin (IL) 1, IL-2, IL-3, IL-4 and gamma interferon). Used for site-specific targeted delivery.

ADVANTAGE - Efficiently adsorb biologically active macromolecules such as DNA, polypeptides, **antigens** and adjuvants. Capable of adsorbing wide variety of macromolecules. Flexible delivery systems, particularly for drugs that are highly sensitive and difficult to formulate.
Dwg.0/0

L16 ANSWER 2 OF 17 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
 ACCESSION NUMBER: 2000-236702 [20] WPIDS
 CROSS REFERENCE: 1988-121200 [18]; 1989-272277 [38]; 1996-189757 [20]; 1998-530832 [45]; 1998-541706 [46]; 1998-567595 [48]; 1999-094826 [08]; 1999-526186 [44]
 DOC. NO. CPI: C2000-071978
 TITLE: Microcapsule and **antigen** compositions for potentiating immune responses mediated by Peyer's patches and useful for vaccinating against a variety of allergens and microbial pathogens.
 DERWENT CLASS: A96 B04 B07 D16
 INVENTOR(S): ELDRIDGE, J H; GILLEY, R M; STAAS, J K; TICE, T R

09/386266

PATENT ASSIGNEE(S): (SOUR) SOUTHERN RES INST; (UABR-N) UAB RES FOUND
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6024983	A	20000215	(200020)*		24

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 6024983	A	CIP of	US 1986-923159 19861024
		CIP of	US 1988-169973 19880318
		CIP of	US 1989-325193 19890316
		Cont of	US 1990-629138 19901218
			US 1993-116802 19930907

FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 6024983	A CIP of	US 5075109

PRIORITY APPLN. INFO: US 1990-629138 19901218; US 1986-923159
19861024; US 1988-169973 19880318; US
1989-325193 19890316; US 1993-116802 19930907

AN 2000-236702 [20] WPIDS

CR 1988-121200 [18]; 1989-272277 [38]; 1996-189757 [20]; 1998-530832
[45]; 1998-541706 [46]; 1998-567595 [48]; 1999-094826 [08];
1999-526186 [44]

AB US 6024983 A UPAB: 20000426

NOVELTY - Microcapsule compositions comprising **antigens**
for potentiating immune responses mediated by Peyer's patches (also
called folliculi lymphatici aggregati), are new.

DETAILED DESCRIPTION - A composition (I) for potentiating an
immune response in an animal, comprising 2 sets of biocompatible
microcapsules (1 - 10 μ m in diameter) containing 2 bioactive
agents encapsulated in biocompatible excipients. The first set of
microcapsules (Ia) provide a primary immune response and the second
set (Ib) releases its bioactive agent in a pulsed manner to
potentiate the subsequent immune response.

An INDEPENDENT CLAIM is also included for a method (II) of
preparing (I).

ACTIVITY - Antimicrobial; immunostimulant.

MECHANISM OF ACTION - Vaccine adjuvant or synergist.

Research has shown that microencapsulation results in a
profoundly heightened immune response to the incorporated

antigen or vaccine in numerous experimental systems. An example is provided by the direct comparison of the level and isotype distribution of the circulating antibody response to Staphylococcal enterotoxin B, the causative agent of Staphylococcal food poisoning. Following immunization with either soluble or microencapsulated enterotoxoid. Groups of mice were administered various doses of the toxoid vaccine incorporated in 50:50

poly(DL-lactide-co-glycolide)

microcapsules, or in soluble form, by intraperitoneal (IP) injection. On Days 10 and 20 following immunization, plasma samples were obtained and assayed for antitoxin activity by end-point titration in isotype-specific immunoradiometric assays. The optimal dose of soluble toxoid (25 mu g) elicited a characteristically poor immune response to the toxin which was detected only in the immunoglobulin (Ig)-M isotype. In contrast, the administration of 25 mu g of toxoid incorporated within microcapsules induced not only an IgM response, but an IgG response which was detectable at a plasma dilution of 1/2560 on day 20 post immunization. In addition, larger doses of toxoid could be administered in microencapsulated form without decreasing the magnitude of the response, as was seen with a 50 mu g dose of soluble toxoid. In fact, the measured release achieved with the microcapsules allows for 4 - 5 times the dose to be administered without causing high zone paralysis, resulting in substantially heightened immunity. This adjuvant activity is even more pronounced following secondary and tertiary immunizations.

The Day 20 IgG antitoxin response following secondary immunization was 512 times higher in mice receiving 50 mu g of microencapsulated toxoid than in mice receiving the optimal dose of soluble toxoid. Further, tertiary immunization with the soluble toxoid at its optimal dose was required to raise an antibody response to the toxin which was equivalent to that observed following a single immunization with 100 mu g micrograms of microencapsulated enterotoxoid. Adjuvant activity of equal magnitude has been documented to common laboratory protein **antigens** such as haptened keyhole limpet hemocyanin and influenza virus vaccine.

USE - (I) is used for delivering a bioactive agent that provides/potentiates an immune response in the mucosally associated lymphoreticular tissues (Peyer's patches) of an animal or for parenterally delivering a bioactive agent that potentiates an immune response (claimed). The composition may be used to induce systemic and mucosal immunity to the animal (claimed). The compositions may be used to vaccinate against allergens, viral **antigens**, bacterial **antigens**, protozoan **antigens** or fungal **antigens** such as influenzae **antigens**, Staphylococcus **antigens**, respiratory syncytial **antigens** parainfluenzae **antigens**, Hemophilus influenza **antigens** Bordetella **pertussis**

antigens, *Neisseria gonorrhoea* **antigens**, *Streptococcus pneumoniae* **antigens**, *Plasmodium falciparum* **antigens**, helminthic pathogen **antigens** or **antigens** to vaccinate against allergies. In particular, it is used to vaccinate against influenza virus or Staphylococcal enterotoxin B (claimed).

ADVANTAGE - The microcapsules are capable of passing through the gastrointestinal tract without degradation (claimed). The size of the microcapsules allows them to pass through or be retained in mucosally associated lymphoreticular tissues (claimed). The use of (I) obviates the need for other immunopotentiators.
Dwg.0/4

L16 ANSWER 3 OF 17 TOXLIT

ACCESSION NUMBER: 2000:8406 TOXLIT

DOCUMENT NUMBER: CA-132-199031H

TITLE: Oral vaccine compositions.

AUTHOR: Brayden DJ

SOURCE: (2000). PCT Int. Appl. PATENT NO. 0012124 03/09/2000
(Elan Corporation, PLC).
CODEN: PIXXD2.

PUB. COUNTRY: IRELAND

DOCUMENT TYPE: Patent

FILE SEGMENT: CA

LANGUAGE: English

OTHER SOURCE: CA 132:199031

ENTRY MONTH: 200003

AB Oral vaccine formulations are disclosed having microparticles sized such that at least 50% of the microparticles are less than 5 μm , preferably less than 3 μm , the microparticles contg. **antigen** entrapped or encapsulated, e.g. by a solvent evapn. method, by a biodegradable polymer, e.g. **poly(D, L-lactide-co-glycolide)**. Addnl., oral vaccine formulations are disclosed having nanoparticles sized such that at least 50% of the microparticles are less than 600 nm, preferably less than 500 nm, the nanoparticles contg. **antigen** entrapped or encapsulated, e.g. by a coacervation method, by a biodegradable polymer, e.g. **poly(D, L-lactide-co-glycolide)**. Protective vaccine formulations contg. the B. **pertussis** **antigens** PTd or a combination of PTd and FHA are provided.

L16 ANSWER 4 OF 17 TOXLIT

ACCESSION NUMBER: 2000:127523 TOXLIT

DOCUMENT NUMBER: CA-134-212529Q

TITLE: Encapsulation of conjugate vaccines with *Bordetella pertussis* fimbriae as novel carrier proteins.

AUTHOR: Crowley-Luke A; Sims M; Reddin K; Vincent P; Gorringe

09/386266

CORPORATE SOURCE: A; Hudson M; Robinson A
Centre for Applied Microbiology and Research,
Salisbury
SOURCE: Proc. Int. Symp. Controlled Release Bioact. Mater.,
(2000). Vol. 27th, pp. 554-555.
CODEN: PCRMEY. ISSN. 1022-0178.
PUB. COUNTRY: UNITED KINGDOM
DOCUMENT TYPE: Journal; Journal Article
FILE SEGMENT: CA
LANGUAGE: English
OTHER SOURCE: CA 134:212529
ENTRY MONTH: 200103

AB B. **pertussis** fimbriae were used as carrier proteins to
produce vaccine that would protect against Hib and augment
protection induced against B. **pertussis** disease where
acellular **pertussis** vaccines deficient in fimbriae are
used. Poly(lactide-glycolide) was used for microencapsulation of
antigen.

L16 ANSWER 5 OF 17 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999410154 EMBASE
TITLE: Protection against B. **pertussis** challenge
following parenteral and oral administration of
microparticles loaded with **pertussis**
antigens.
AUTHOR: McClean S.; Conway M.; Mills K.H.G.; Brayden D.J.
CORPORATE SOURCE: D.J. Brayden, Elan Pharmaceutical Technologies,
Trinity College, Dublin 2, Ireland
SOURCE: Proceedings of the Controlled Release Society, (1999)
-/26 (153-154).
Refs: 4
ISSN: 1022-0178 CODEN: 58GMAH
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 004 Microbiology
027 Biophysics, Bioengineering and Medical
Instrumentation
030 Pharmacology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English

L16 ANSWER 6 OF 17 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999186488 EMBASE
TITLE: Single-administration vaccines: Controlled-release
technology to mimic repeated immunizations.
AUTHOR: Cleland J.L.
CORPORATE SOURCE: J.L. Cleland, Pharmaceutical R and D, Genentech, 1

Searcher : Shears 308-4994

DNA Way, South San Francisco, CA 94080, United States. cleland@gene.com

SOURCE: Trends in Biotechnology, (1999) 17/1 (25-29).
Refs: 33
ISSN: 0167-7799 CODEN: TRBIDM

PUBLISHER IDENT.: S 0167-7799(98)01272-4

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 026 Immunology, Serology and Transplantation
037 Drug Literature Index
039 Pharmacy

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The most effective mechanism for the elimination of disease from society is the use of vaccinations, but these often require repeated administration. However, single-administration vaccine formulations provide the repeated administrations automatically. One approach is the development of injectable controlled-release microsphere formulations containing the vaccine **antigen** that is released as a pulse 1-6 months after injection. The time of the pulse is dependent upon the rate of polymer degradation, which is dictated by the polymer's composition and molecular weight. This controlled-release technology may provide complete protection against disease after a single administration. Copyright (C) 1999 Elsevier Science Ltd.

L16 ANSWER 7 OF 17 TOXLIT

ACCESSION NUMBER: 1998:162948 TOXLIT

DOCUMENT NUMBER: CA-130-086184A

TITLE: Vaccines containing Bordetella **pertussis** **antigen**.

AUTHOR: Farrar GH; Jones DH

SOURCE: (1998). PCT Int. Appl. PATENT NO. 9858668 12/30/1998 (Microbiological Research Authority).
CODEN: PIXXD2.

PUB. COUNTRY: UNITED KINGDOM

DOCUMENT TYPE: Patent

FILE SEGMENT: CA

LANGUAGE: English

OTHER SOURCE: CA 130:86184

ENTRY MONTH: 199902

AB A vaccinating conjugate comprises an **antigen** conjugated to a carrier selected from Bordetella **pertussis** fimbria, **pertussis** toxin, **pertussis** toxoid, and **pertussis** 69kD protein. The conjugate may also comprise a second **antigen**, different from the first. An oral vaccinating compn. comprises Bordetella **pertussis** fimbria or fimbria-**antigen** conjugate.

L16 ANSWER 8 OF 17 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 ACCESSION NUMBER: 1999016458 EMBASE
 TITLE: Approaches to new vaccines.
 AUTHOR: Mahon B.P.; Moore A.; Johnson P.A.; Mills K.H.G.
 CORPORATE SOURCE: B.P. Mahon, Infection and Immunity Group, National
 University of Ireland, Maynooth, County Kildare,
 Ireland
 SOURCE: Critical Reviews in Biotechnology, (1998) 18/4
 (257-282).
 Refs: 161
 ISSN: 0738-8551 CODEN: CRBTE5
 COUNTRY: United States
 DOCUMENT TYPE: Journal; General Review
 FILE SEGMENT: 026 Immunology, Serology and Transplantation
 027 Biophysics, Bioengineering and Medical
 Instrumentation
 037 Drug Literature Index
 038 Adverse Reactions Titles
 039 Pharmacy
 LANGUAGE: English
 SUMMARY LANGUAGE: English

AB The explosive technological advances in the fields of immunology and molecular biology in the last 5 years had an enormous impact on the identification of candidate vaccines against diseases, which until a few years ago seemed uncontrollable. Increased knowledge of the immune system has helped to define the mechanisms that underlie successful immunization and is now being exploited to develop improved versions of existing vaccines and new vaccines against emerging pathogens, tumors, or autoimmune diseases. An understanding of the mechanisms of action of novel adjuvants and the development of new vector and delivery systems will have a major impact on vaccine strategies. The use of DNA encoding **antigens** from pathogenic viruses, bacteria, and parasites as vaccines is a new approach that is receiving considerable attention. This and other innovative approaches, including vaccine production in plants, are appraised in this review. The successful eradication of smallpox and the imminent eradication of poliomyelitis by worldwide immunization campaigns provide positive examples of how the vaccine-mediated approach can lead to disease elimination; with the advent of new vaccines and improved delivery systems, there is no scientific reason why these successes cannot be repeated.

L16 ANSWER 9 OF 17 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 ACCESSION NUMBER: 1998131449 EMBASE
 TITLE: Oral and nasal immunization with microencapsulated
 clinically relevant proteins.
 AUTHOR: Alpar H.O.; Eyles J.E.; Williamson E.D.

CORPORATE SOURCE: H.O. Alpar, Pharmaceutical Sciences Institute, Aston University, Aston Triangle, Birmingham B4 7ET, United Kingdom

SOURCE: S.T.P. Pharma Sciences, (1998) 8/1 (31-39).

Refs: 73

ISSN: 1157-1489 CODEN: STSSE5

COUNTRY: France

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
039 Pharmacy

LANGUAGE: English

SUMMARY LANGUAGE: French

AB Recently, much interest has been focused on the significance of inducing not only systemic immunity, but also effective local immunity at susceptible mucosal surfaces. A new field of mucosal immunity has been established as information accumulates on mucosa-associated lymphoid tissue and on its role in both local and systemic immune responses. This article focuses directly on the use of microparticulate carriers to achieve effective mucosal immunization. The immunology of the mucosal immune system has been comprehensively reviewed elsewhere, and as such only key issues in conjunction with recent experiments which relate to mucosal immunization with microparticulate carriers will be addressed here.

L16 ANSWER 10 OF 17 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1998131448 EMBASE

TITLE: Towards a multipurpose mucosal vaccination using phosphorylcholine as a unique **antigen**?

AUTHOR: Trolle S.; Andreumont A.; Fattal E.

CORPORATE SOURCE: E. Fattal, Lab. Physic. Pharmacotech. Biopharm., URA-CNRS 1218, Faculte de Pharmacie, 92296 Chatenay-Malabry Cedex, France

SOURCE: S.T.P. Pharma Sciences, (1998) 8/1 (19-30).

Refs: 112

ISSN: 1157-1489 CODEN: STSSE5

COUNTRY: France

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
039 Pharmacy

LANGUAGE: English

SUMMARY LANGUAGE: French

AB Intestinal and pulmonary bacterial infections are a major cause of worldwide child mortality. The development of a sole plurispecific vaccine against those infections is a World Health Organization

priority. In that respect, we hypothesized that immunization with phosphorylcholine, a ubiquitous **antigen** present on different pathogenic microorganisms, might be an original approach. Our vaccine is constituted of phosphorylcholine coupled to a protein carrier and entrapped in biodegradable microspheres. This vaccine is stable and adequate for oral or intranasal immunization and thus for the stimulation of the common mucosal immune system. Vaccinated animals were statistically protected against either a lethal oral challenge by *Salmonella typhimurium*, or a lethal nasal challenge by *Streptococcus pneumoniae*. The results constitute a strong impetus to explore the potentialities of our candidate vaccine.

L16 ANSWER 11 OF 17 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1998036607 EMBASE

TITLE: Conference Science Medal 1997 lecture at British Pharmaceutical Conference, Scarborough, United Kingdom, September 15-18, 1997: Recent advances in vaccine adjuvants for systemic and mucosal administration.

AUTHOR: O'Hagan D.T.

CORPORATE SOURCE: D.T. O'Hagan, Chiron Corporation, 4560 Horton Street, Emeryville, CA 947608, United States

SOURCE: Journal of Pharmacy and Pharmacology, (1998) 50/1 (1-10).

Refs: 57

ISSN: 0022-3573 CODEN: JPPMAB

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Conference Article

FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Although vaccines produced by recombinant DNA technology are safer than traditional vaccines, which are based on attenuated or inactivated bacteria or viruses, they are often poorly immunogenic. Therefore, adjuvants are often required to enhance the immunogenicity of these vaccines. A number of adjuvants which are particulates of defined dimensions ($< 5 \mu\text{m}$) have been shown to be effective in enhancing the immunogenicity of weak **antigens** in animal models. Two novel adjuvants which possess significant potential for the development of new vaccines include an oil-in-water microemulsion (MF59) and polymeric microparticles. MF59 has been shown to be a potent and safe adjuvant in human subjects with several vaccines (for example HSV-2, HIV-1 and influenza virus). An MF59 adjuvanted influenza has been recommended for approval in Italy. Microparticles prepared from the biodegradable

polymers the poly(lactide-co-glycolides) (PLG) are currently undergoing extensive pre-clinical evaluation as vaccine adjuvants. Because of their controlled release characteristics, microparticles also possess considerable potential for the development of single dose vaccines. The development of single dose vaccines would offer significant advantages and would improve vaccination uptake rates in at risk populations, particularly in the developing world. In addition to systemic administration, microparticles have also been shown to enhance the immunogenicity of vaccines when administered by mucosal routes. Therefore microparticles may allow the development of novel vaccines which can be administered by non-parenteral routes. Mucosal administration of vaccines would significantly improve patient compliance by allowing immunization to be achieved without the use of needles. An alternative approach to the development of mucosally administered vaccines involves the production of genetically detoxified toxins. Heat labile enterotoxin (LT) from *Escherichia coli* and cholera toxin from *Vibrio cholerae* are two closely related bacterially produced toxins, which are the most potent adjuvants available. However, these molecules are too toxic to be used in the development of human vaccines. Nevertheless, these toxins have been modified by site-directed mutagenesis to produce molecules which are adjuvant active, but non-toxic. The most advanced of these molecules (LTK63), which has a single amino acid substitution in the enzymatically active subunit of LT, is active as an adjuvant, but non-toxic in pre-clinical models. The approach of genetically detoxifying bacterial toxins to produce novel adjuvants offers significant potential for the future development of mucosally administered vaccines.

L16 ANSWER 12 OF 17 MEDLINE DUPLICATE 1
 ACCESSION NUMBER: 96351451 MEDLINE
 DOCUMENT NUMBER: 96351451 PubMed ID: 8717383
 TITLE: Poly(lactide-co-glycolide) microencapsulation of vaccine **antigens**.
 AUTHOR: Jones D H; McBride B W; Farrar G H
 CORPORATE SOURCE: Microbial Antigens Department, Centre for Applied Microbiology and Research, Salisbury, Wilts, UK.
 SOURCE: JOURNAL OF BIOTECHNOLOGY, (1996 Jan 26) 44 (1-3) 29-36.
 Journal code: AL6; 8411927. ISSN: 0168-1656.
 PUB. COUNTRY: Netherlands
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: B
 ENTRY MONTH: 199610
 ENTRY DATE: Entered STN: 19961025
 Last Updated on STN: 19961025

Entered Medline: 19961016

AB Fimbriae from *Bordetella pertussis* have been encapsulated in poly(lactide-co-glycolide) (PLG) microspheres of a size appropriate for oral administration. The binding of antibodies which react with conformational or linear fimbrial epitopes, to fimbriae released from microspheres, suggested that the process of was not detrimental to the native integrity of the protein. Mice were immunised by oral gavage with a single dose of microencapsulated fimbriae, or with fimbriae adsorbed onto alhydrogel and administered by intraperitoneal injection. The resulting immune responses in serum were comparable but only oral administration of microencapsulated fimbriae elicited specific immune responses in external secretions. Six weeks after immunisation, both groups of immunised animals were protected against challenge with live *B. pertussis*.

L16 ANSWER 13 OF 17 TOXLINE

ACCESSION NUMBER: 1996:1668 TOXLINE
 DOCUMENT NUMBER: CRISP-96-AI33544-04
 TITLE: MICROSPHERES TO ENHANCE VACCINE IMMUNOGENICITY.
 AUTHOR: MICHALEK S M
 CORPORATE SOURCE: UNIVERSITY OF ALABAMA, UAB STATION, ZRB 437,
 BIRMINGHAM, AL 35294-0007
 U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC
 HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL
 INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES.
 CONTRACT NUMBER: 5R01AI33544-04
 SOURCE: (1995). Crisp Data Base National Institutes Of
 Health. Award Type: G = Grant
 PUB. COUNTRY: United States
 DOCUMENT TYPE: (RESEARCH)
 FILE SEGMENT: CRISP
 LANGUAGE: English
 ENTRY MONTH: 199604

AB RPROJ/CRISP One of the major impediments to immunizing the world's children with a protective course of vaccinations against childhood diseases is the requirement for a complex course of booster immunizations. It has become clear that a significant proportion of this target population does not complete the full immunization regimen because of the number of clinic visits required. The primary goal of this proposal is to develop microencapsulated formulations of the current diphtheria, acellular *pertussis*, tetanus and *Haemophilus influenza* type B vaccines which will replace the pediatric vaccination series with a single injection at 2 months of age. The vaccines will be individually microencapsulated in poly(DL-lactide-co-glycolide) (DL- PLG), a biodegradable and biocompatible polyester which is approved for human use. Our

studies have shown that the delivery of protein and glycoprotein-based vaccines in DL-**PLG** microspheres strongly potentiates antibody responses. The antibody responses in mice to the microencapsulated vaccines will be measured by ELISA, and the protective efficacy of the responses tested in in vitro neutralization and bactericidal assays and in in vivo protection from lethal challenge studies. The biodegradation rate of DL-**PLGs** is determined by the ratio of **lactide** -to-glycolide in the copolymers. Thus, Vaccine-microspheres with different DL-**PLGs** release at different times after injection, and may be co-injected to deliver discrete pulses of vaccine which function as primary and booster immunizations. Each of the vaccines will be encapsulated in a series of DL-**PLGs** designed to release vaccine pulses which mimic the current 2, 4, 6 and 15-19 month immunization schedule after a single injection. The single injection pulse-release mixture of microencapsulated vaccines will be evaluated for appropriate booster responses, protective efficacy, absence of vaccine cross interference and stability with time and increased temperature.

L16 ANSWER 14 OF 17 MEDLINE

DUPLICATE 2

ACCESSION NUMBER: 95197236 MEDLINE
 DOCUMENT NUMBER: 95197236 PubMed ID: 7890372
 TITLE: Adjuvanticity and protective immunity elicited by Bordetella **pertussis** antigens encapsulated in poly(DL-**lactide**-co-glycolide) microspheres.
 AUTHOR: Shahin R; Leef M; Eldridge J; Hudson M; Gilley R
 CORPORATE SOURCE: Laboratory of Pertussis, Food and Drug Administration, Bethesda, Maryland 20892-4555.
 SOURCE: INFECTION AND IMMUNITY, (1995 Apr) 63 (4) 1195-200.
 Journal code: GO7; 0246127. ISSN: 0019-9567.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199504
 ENTRY DATE: Entered STN: 19950427
 Last Updated on STN: 19950427
 Entered Medline: 19950420

AB Purified Bordetella **pertussis** antigens, encapsulated in biodegradable poly(DL-**lactide**-co-glycolide) (DL-**PLG**) microspheres, were evaluated for their immunogenicity and ability to elicit a protective immune response against B. **pertussis** respiratory infection. Microencapsulated **pertussis** toxoid, filamentous hemagglutinin, and pertactin all retained their immunogenicity when administered parenterally. Intranasal

immunization with a low dose (1 micrograms) of encapsulated filamentous hemagglutinin, **pertussis** toxoid, or pertactin elicited strong specific immunoglobulin G and immunoglobulin A antibody responses in respiratory secretions that were greater in magnitude than the responses elicited by the same doses of unencapsulated **antigen**. Intranasal immunization with as little as 1 micrograms of encapsulated **pertussis antigen** prior to infection reduced the bacterial recovery by 3 log₁₀ CFU. However, intranasal immunization with the same low doses of unencapsulated **antigens** did not reduce infection. Intranasal administration of a combination of 1 micrograms of each of the microencapsulated **pertussis antigens** was more effective in reducing bacterial infection than administration of any single microencapsulated **antigen**. Intranasal administration of microencapsulated B. **pertussis antigens** elicits high levels of specific antibody coinciding with protection against infection when these microspheres are administered to the respiratory tract. These data provide evidence of the respiratory adjuvanticity of three different DL-PLC microsphere preparations, each of which contains a unique B. **pertussis antigen**.

L16 ANSWER 15 OF 17 TOXLINE

ACCESSION NUMBER: 1995:205933 TOXLINE

DOCUMENT NUMBER: CRISP-95-AI33544-03

TITLE: MICROSPHERES TO ENHANCE VACCINE IMMUNOGENICITY.

AUTHOR: MICHALEK S M

CORPORATE SOURCE: UNIVERSITY OF ALABAMA, UAB STATION, ZRB 437,
BIRMINGHAM, AL 35294-0007
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC
HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL
INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES.

CONTRACT NUMBER: 5R01AI33544-03

SOURCE: (1994). Crisp Data Base National Institutes Of
Health. Award Type: G = Grant

PUB. COUNTRY: United States

DOCUMENT TYPE: (RESEARCH)

FILE SEGMENT: CRISP

LANGUAGE: English

ENTRY MONTH: 199507

AB RPROJ/CRISP One of the major impediments to immunizing the world's children with a protective course of vaccinations against childhood diseases is the requirement for a complex course of booster immunizations. It has become clear that a significant proportion of this target population does not complete the full immunization regimen because of the number of clinic visits required. The primary goal of this proposal is to develop microencapsulated formulations of the current diphtheria, acellular **pertussis**

, tetanus and Haemophilus influenza type B vaccines which will replace the pediatric vaccination series with a single injection at 2 months of age. The vaccines will be individually microencapsulated in **poly(DL-lactide-co-glycolide)** (DL- **PLG**), a biodegradable and biocompatible polyester which is approved for human use. Our studies have shown that the delivery of protein and glycoprotein-based vaccines in DL-**PLG** microspheres strongly potentiates antibody responses. The antibody responses in mice to the microencapsulated vaccines will be measured by ELISA, and the protective efficacy of the responses tested in in vitro neutralization and bactericidal assays and in in vivo protection from lethal challenge studies. The biodegradation rate of DL-**PLGs** is determined by the ratio of **lactide**-to-glycolide in the copolymers. Thus, Vaccine-microspheres with different DL-**PLGs** release at different times after injection, and may be co-injected to deliver discrete pulses of vaccine which function as primary and booster immunizations. Each of the vaccines will be encapsulated in a series of DL-**PLGs** designed to release vaccine pulses which mimic the current 2, 4, 6 and 15-19 month immunization schedule after a single injection. The single injection pulse-release mixture of microencapsulated vaccines will be evaluated for appropriate booster responses, protective efficacy, absence of vaccine cross interference and stability with time and increased temperature.

L16 ANSWER 16 OF 17 TOXLINE

ACCESSION NUMBER: 1994:53540 TOXLINE

DOCUMENT NUMBER: CRISP-94-AI33544-02

TITLE: MICROSPHERES TO ENHANCE VACCINE IMMUNOGENICITY.

AUTHOR: MICHALEK S M

CORPORATE SOURCE: UNIVERSITY OF ALABAMA, UAB STATION, ZRB 437,
BIRMINGHAM, AL 35294-0007
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC
HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL
INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES.

CONTRACT NUMBER: 5R01AI33544-02

SOURCE: (1993). Crisp Data Base National Institutes Of
Health. Award Type: G = Grant

PUB. COUNTRY: United States

DOCUMENT TYPE: (RESEARCH)

FILE SEGMENT: CRISP

LANGUAGE: English

ENTRY MONTH: 199403

AB RPROJ/CRISP One of the major impediments to immunizing the world's children with a protective course of vaccinations against childhood diseases is the requirement for a complex course of booster immunizations. It has become clear that a significant proportion of

this target population does not complete the full immunization regimen because of the number of clinic visits required. The primary goal of this proposal is to develop microencapsulated formulations of the current diphtheria, acellular **pertussis**, tetanus and Haemophilus influenza type B vaccines which will replace the pediatric vaccination series with a single injection at 2 months of age. The vaccines will be individually microencapsulated in **poly(DL-lactide-co-glycolide)** (DL- **PLG**), a biodegradable and biocompatible polyester which is approved for human use. Our studies have shown that the delivery of protein and glycoprotein-based vaccines in DL-**PLG** microspheres strongly potentiates antibody responses. The antibody responses in mice to the microencapsulated vaccines will be measured by ELISA, and the protective efficacy of the responses tested in in vitro neutralization and bactericidal assays and in in vivo protection from lethal challenge studies. The biodegradation rate of DL-**PLGs** is determined by the ratio of **lactide**-to-glycolide in the copolymers. Thus, Vaccine-microspheres with different DL-**PLGs** release at different times after injection, and may be co-injected to deliver discrete pulses of vaccine which function as primary and booster immunizations. Each of the vaccines will be encapsulated in a series of DL-**PLGs** designed to release vaccine pulses which mimic the current 2, 4, 6 and 15-19 month immunization schedule after a single injection. The single injection pulse-release mixture of microencapsulated vaccines will be evaluated for appropriate booster responses, protective efficacy, absence of vaccine cross interference and stability with time and increased temperature.

L16 ANSWER 17 OF 17 TOXLINE

ACCESSION NUMBER: 1994:53539 TOXLINE
 DOCUMENT NUMBER: CRISP-94-AI33544-01
 TITLE: MICROSPHERES TO ENHANCE VACCINE IMMUNOGENICITY.
 AUTHOR: EDLRIDGE J H
 CORPORATE SOURCE: UNIVERSITY OF ALABAMA, UAB STATION, ZRB 437,
 BIRMINGHAM, AL 35294-0007
 U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC
 HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL
 INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES.
 CONTRACT NUMBER: 1R01AI33544-01
 SOURCE: (1992). Crisp Data Base National Institutes Of
 Health. Award Type: G = Grant
 PUB. COUNTRY: United States
 DOCUMENT TYPE: (RESEARCH)
 FILE SEGMENT: CRISP
 LANGUAGE: English
 ENTRY MONTH: 199403

Searcher : Shears 308-4994

AB RPROJ/CRISP One of the major impediments to immunizing the world's children with a protective course of vaccinations against childhood diseases is the requirement for a complex course of booster immunizations. It has become clear that a significant proportion of this target population does not complete the full immunization regimen because of the number of clinic visits required. The primary goal of this proposal is to develop microencapsulated formulations of the current diphtheria, acellular **pertussis**, tetanus and Haemophilus influenza type B vaccines which will replace the pediatric vaccination series with a single injection at 2 months of age. The vaccines will be individually microencapsulated in **poly(DL-lactide-co-glycolide)** (DL- **PLG**), a biodegradable and biocompatible polyester which is approved for human use. Our studies have shown that the delivery of protein and glycoprotein-based vaccines in DL-**PLG** microspheres strongly potentiates antibody responses. The antibody responses in mice to the microencapsulated vaccines will be measured by ELISA, and the protective efficacy of the responses tested in in vitro neutralization and bactericidal assays and in in vivo protection from lethal challenge studies. The biodegradation rate of DL-**PLGs** is determined by the ratio of **lactide**-to-glycolide in the copolymers. Thus, Vaccine-microspheres with different DL-**PLGs** release at different times after injection, and may be co-injected to deliver discrete pulses of vaccine which function as primary and booster immunizations. Each of the vaccines will be encapsulated in a series of DL-**PLGs** designed to release vaccine pulses which mimic the current 2, 4, 6 and 15-19 month immunization schedule after a single injection. The single injection pulse-release mixture of microencapsulated vaccines will be evaluated for appropriate booster responses, protective efficacy, absence of vaccine cross interference and stability with time and increased temperature.

(FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO, TOXLIT, TOXLINE, PHIC, PHIN' ENTERED AT 15:08:27 ON 04 JUN 2001)

L17 13 S BRAYDEN D?/AU AND (L4 OR L6 OR L7) ✓

L18 7 DUP REM L17 (6 DUPLICATES REMOVED)

L18 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1

ACCESSION NUMBER: 2001:146645 CAPLUS

TITLE: Protection against Bordetella pertussis infection following parenteral or oral immunization with antigens entrapped in biodegradable particles: effect of formulation and route of immunization on induction of Th1 and Th2 cells

AUTHOR(S): Conway, M. A.; Madrigal-Estebas, L.; McClean,

CORPORATE SOURCE: S.; **Brayden, D. J.**; Mills, K. H. G.
 Department of Biology, Institute of Immunology,
 Infection and Immunity Group, National
 University of Ireland, Maynooth, Ire.

SOURCE: Vaccine (2001), 19(15-16), 1940-1950
 CODEN: VACCDE; ISSN: 0264-410X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The immunogenicity and protective efficacy of systemically and orally delivered pertussis antigens entrapped in either microparticle poly-lactide-co-glycolide (PLG) or nanoparticle PLG formulations were evaluated in a murine respiratory challenge model for infection with Bordetella pertussis. The results demonstrate that immunization with two parenteral doses of 1 .mu.g or three oral doses of 100 .mu.g of pertussis toxoid (PTd) and filamentous haemagglutinin (FHA) encapsulated in PLG conferred a high level of protection against B. pertussis challenge. Furthermore protection could be generated with a single parenteral immunization with a combined microparticle and nanoparticle formulation. However, the route of immunization and the size of the particles affected the type of T cell response induced. Parenteral immunization with PTd and FHA entrapped in PLG microparticles elicits a potent type 1 T cell response and potent antibody response when given by the i.p. (i.p.) or i.m. (i.m.) route. In contrast, nanoparticle formulations favored the induction of Th2 cells.

REFERENCE COUNT: 39

REFERENCE(S): (1) Ausiello, C; Infect Immun 1997, V65, P2168
 CAPLUS
 (2) Bazin, H; J Immunol 1970, V105, P1049 CAPLUS
 (4) Bomford, R; AIDS Res Hum Retrovir 1992, V8,
 P1765 CAPLUS
 (7) Cahill, E; Vaccine 1995, V13, P455 CAPLUS
 (8) Challacombe, S; Immunology 1992, V76, P164
 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 2

ACCESSION NUMBER: 2000:161163 CAPLUS

DOCUMENT NUMBER: 132:199032

TITLE: Method for inducing a cell-mediated immune
 response and parenteral vaccine formulations
 therefor

INVENTOR(S): **Brayden, David James**

PATENT ASSIGNEE(S): Elan Corporation, PLC, Ire.

SOURCE: PCT Int. Appl., 68 pp.
 CODEN: PIXXD2

DOCUMENT TYPE: Patent

09/386266

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012125	A1	20000309	WO 1999-IE87	19990831
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9954412	A1	20000321	AU 1999-54412	19990831
PRIORITY APPLN. INFO.:			US 1998-98760	P 19980901
			WO 1999-IE87	W 19990831

AB A method of inducing either a TH1 polarized immune response, a TH2 polarized immune response, or a combined TH1 and TH2 response to an antigen, and assocd. vaccine formulations, are disclosed. A method is provided for inducing a polarized TH1 response by parenteral administration of microparticles sized such that at least 50% of the microparticles are less than 5 .mu.m, the microparticles contg. antigen entrapped or encapsulated by a biodegradable polymer. Addnl., a method is provided for inducing a polarized TH2 response by parenteral administration of nanoparticles sized such that at least 50% of the nanoparticles are less than 600 nm, the nanoparticles contg. antigen entrapped or encapsulated by a biodegradable polymer. Vaccine formulations contg. the B. pertussis antigens PTd, FHA, or a combination of PTd and FHA, are provided.

REFERENCE COUNT: 11

REFERENCE(S):

- (1) Cahill, E; VACCINE 1995, V13(5), P455 CAPLUS
- (2) Cohen, S; "Microparticulate Systems for the Delivery of Proteins and Vaccines 1996, P51 CAPLUS
- (3) Farrar Graham Henry; WO 9858668 A 1998 CAPLUS
- (4) Jones, D; INFECTION AND IMMUNITY 1996, V64(2), P489 CAPLUS
- (6) Medeva Holdings Bv; WO 9321950 A 1993 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 3
 ACCESSION NUMBER: 2000:161162 CAPLUS
 DOCUMENT NUMBER: 132:199031
 TITLE: Oral vaccine compositions

Searcher : Shears 308-4994

INVENTOR(S): **Brayden, David James**
 PATENT ASSIGNEE(S): Elan Corporation, PLC, Ire.
 SOURCE: PCT Int. Appl., 52 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012124	A1	20000309	WO 1999-IE86	19990831

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR,
 CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
 ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
 LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD,
 SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU,
 ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE,
 DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
 CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9954411	A1	20000321	AU 1999-54411	19990831
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PRIORITY APPLN. INFO.:	US 1998-98759	P	19980901
	WO 1999-IE86	W	19990831

AB Oral vaccine formulations are disclosed having microparticles sized such that at least 50% of the microparticles are less than 5 .mu.m, preferably less than 3 .mu.m, the microparticles contg. antigen entrapped or encapsulated, e.g. by a solvent evapn. method, by a biodegradable polymer, e.g. **poly(D,L-lactide-co-glycolide)**. Addnl., oral vaccine formulations are disclosed having nanoparticles sized such that at least 50% of the microparticles are less than 600 nm, preferably less than 500 nm, the nanoparticles contg. antigen entrapped or encapsulated, e.g. by a coacervation method, by a biodegradable polymer, e.g. **poly(D,L-lactide-co-glycolide)**. Protective vaccine formulations contg. the B. pertussis antigens PTd or a combination of PTd and FHA are provided.

REFERENCE COUNT: 9

REFERENCE(S): (1) Cahill, E; VACCINE 1995, V13(5), P455 CAPLUS
 (2) Desai, M; PHARMACEUTICAL RESEARCH 1996, V13(12), P1838 CAPLUS
 (3) Henry, F; WO 9858668 A 1998 CAPLUS
 (4) Jones, D; INFECTION AND IMMUNITY 1996, V64(2), P489 CAPLUS
 (5) Medeva Holdings Bv; WO 9321950 A 1993 CAPLUS
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

Searcher : Shears 308-4994

L18 ANSWER 4 OF 7 TOXLIT
 ACCESSION NUMBER: 2000:8407 TOXLIT
 DOCUMENT NUMBER: CA-132-199032J
 TITLE: Method for inducing a cell-mediated immune response and parenteral vaccine formulations therefor.
 AUTHOR: **Brayden DJ**
 SOURCE: (2000). PCT Int. Appl. PATENT NO. 0012125 03/09/2000 (Elan Corporation, PLC).
 CODEN: PIXXD2.
 PUB. COUNTRY: IRELAND
 DOCUMENT TYPE: Patent
 FILE SEGMENT: CA
 LANGUAGE: English
 OTHER SOURCE: CA 132:199032
 ENTRY MONTH: 200003

AB A method of inducing either a TH1 polarized immune response, a TH2 polarized immune response, or a combined TH1 and TH2 response to an antigen, and assocd. vaccine formulations, are disclosed. A method is provided for inducing a polarized TH1 response by parenteral administration of microparticles sized such that at least 50% of the microparticles are less than 5 .mu.m, the microparticles contg. antigen entrapped or encapsulated by a biodegradable polymer. Addnl., a method is provided for inducing a polarized TH2 response by parenteral administration of nanoparticles sized such that at least 50% of the nanoparticles are less than 600 nm, the nanoparticles contg. antigen entrapped or encapsulated by a biodegradable polymer. Vaccine formulations contg. the B. pertussis antigens PTd, FHA, or a combination of PTd and FHA, are provided.

L18 ANSWER 5 OF 7 TOXLIT
 ACCESSION NUMBER: 2000:8406 TOXLIT
 DOCUMENT NUMBER: CA-132-199031H
 TITLE: Oral vaccine compositions.
 AUTHOR: **Brayden DJ**
 SOURCE: (2000). PCT Int. Appl. PATENT NO. 0012124 03/09/2000 (Elan Corporation, PLC).
 CODEN: PIXXD2.
 PUB. COUNTRY: IRELAND
 DOCUMENT TYPE: Patent
 FILE SEGMENT: CA
 LANGUAGE: English
 OTHER SOURCE: CA 132:199031
 ENTRY MONTH: 200003

AB Oral vaccine formulations are disclosed having microparticles sized such that at least 50% of the microparticles are less than 5 .mu.m, preferably less than 3 .mu.m, the microparticles contg. antigen entrapped or encapsulated, e.g. by a solvent evapn. method, by a biodegradable polymer, e.g. poly(D,L-

lactide-co-glycolide). Addnl., oral vaccine formulations are disclosed having nanoparticles sized such that at least 50% of the microparticles are less than 600 nm, preferably less than 500 nm, the nanoparticles contg. antigen entrapped or encapsulated, e.g. by a coacervation method, by a biodegradable polymer, e.g. **poly(D,L-lactide-co-glycolide)**. Protective vaccine formulations contg. the B. pertussis antigens PTd or a combination of PTd and FHA are provided.

L18 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 4
 ACCESSION NUMBER: 1999:722187 CAPLUS
 DOCUMENT NUMBER: 132:255890
 TITLE: Protection against B. pertussis challenge following parenteral and oral administration of microparticles loaded with pertussis antigens
 AUTHOR(S): McClean, S.; Conway, M.; Mills, K. H. G.; **Brayden, D. J.**
 CORPORATE SOURCE: Elan Pharmaceutical Technologies, Dublin, 2, Ire.
 SOURCE: Proc. Int. Symp. Controlled Release Bioact. Mater. (1999), 26th, 153-154
 CODEN: PCRMEY; ISSN: 1022-0178
 PUBLISHER: Controlled Release Society, Inc.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Administration of pertussis toxin and filamentous hemagglutinin entrapped in glycolide-**lactide** copolymer (PLG) microparticles provides protective immunity after either oral or parenteral immunization. I.p. immunization with PLG-entrapped antigens resulted in a distinct TH1 response, which has the potential for the development of vaccines against diseases caused by intracellular organisms.
 REFERENCE COUNT: 4
 REFERENCE(S): (1) Mills; Infect Immun 1993, V61, P339
 (2) Mills; Infect Immun 1997, V66, P594
 (3) Moore; Vaccine 1995, V13, P1741 CAPLUS
 (4) Ramtoola; J Microencap 1992, V9, P415 CAPLUS

L18 ANSWER 7 OF 7 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 ACCESSION NUMBER: 1998119382 EMBASE
 TITLE: Binding and uptake of biodegradable poly-DL-lactide micro- and nanoparticles in intestinal epithelia.
 AUTHOR: McClean S.; Prosser E.; Meehan E.; O'Malley D.; Clarke N.; Ramtoola Z.; **Brayden D.**
 CORPORATE SOURCE: S. McClean, Elan Pharmaceutical Technologies, Biotechnology Building, Trinity College, Dublin 2, Ireland

09/386266

SOURCE: European Journal of Pharmaceutical Sciences, (1998)
6/2 (153-163).

Refs: 30

ISSN: 0928-0987 CODEN: EPSCED

PUBLISHER IDENT.: S 0928-0987(97)10007-0

COUNTRY: Netherlands

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SUMMARY LANGUAGE: English

AB The use of biodegradable particles as oral delivery vehicles for macromolecular drugs was investigated. We evaluated the binding, uptake and absorption of poly-DL-lactide (PLA) micro- and nanoparticles in Caco-2 monolayers and in ileal tissue and gut associated lymphoid tissue (GALT) of anaesthetised rats and rabbits. Using a range of experimental techniques, we found that approximately 10% of administered micro- and nanoparticles were adsorbed to the apical membranes of each of the five intestinal models. Nanoparticles were found to be absorbed better than microparticles. Overall, little discrimination in uptake patterns was evident between Peyer's patch (PP) and non-PP tissue while rat ileum showed a greater uptake capacity than rabbit. Our results show that uptake of PLA particles was low capacity, size- dependent and predominantly transcellular in all systems. A low proportion of the apically-bound particles was absorbed, with uptake exclusion evident for particles >4.µm. The affinity of PLA particles for intestinal epithelia and GALT needs to be greatly enhanced in order to achieve improved oral bioavailability of macromolecules.

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